Gold-Catalyzed *cis*-Hydroarylation of Ynamides with Indoles: Regio- and Stereoselective Synthesis of a class of 2-Vinylindoles

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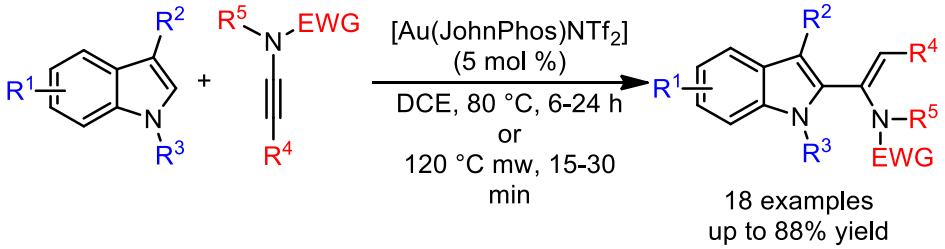
Supporting Information Placeholder

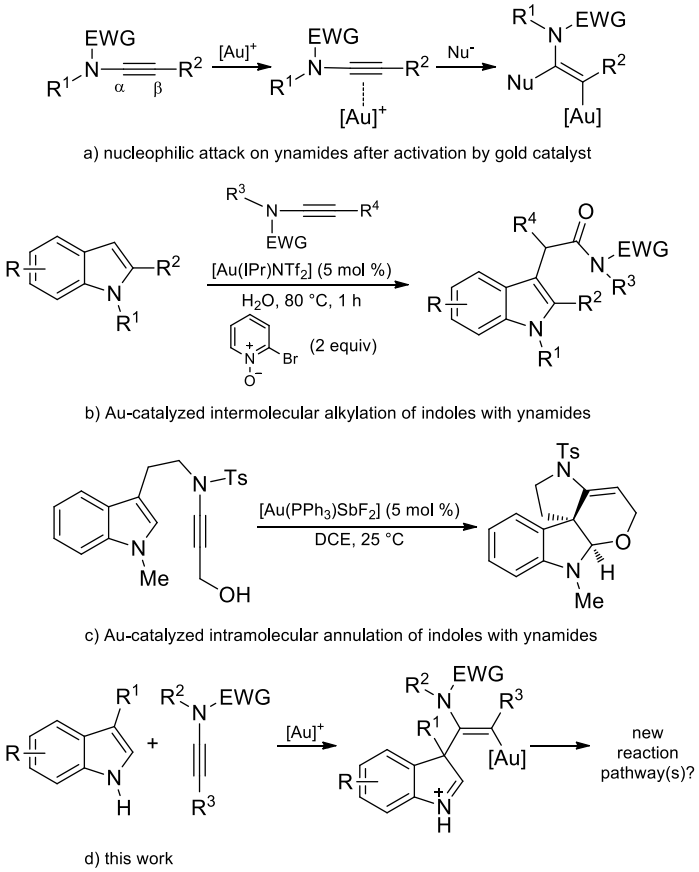


ABSTRACT: A new gold-catalyzed reaction of ynamides with 3-substituted indoles as nucleophiles is reported. The reaction allows for the synthesis of a new class of 2-vinylindole derivatives in good yields *via* the intermediacy of a cyclopropyl gold-carbenoid species.

Over the past twenty years, among unsaturated compounds, ynamides have emerged as simple, small and versatile building blocks in organic synthesis.[1] Ynamides are structurally characterized by the presence of an electron donor nitrogen atom directly connected to a C_{sp} atom of an alkyne. Subsequent strong polarization of the triple bond enhances alkyne reactivity towards electrophiles and the resulting keteniminium ions can be trapped by suitable carbon- and hetero-nucleophiles and/or involved in cycloaddition and cyclization reactions. Moreover, the disclosed high reactivity is often accompanied by high level of regio- and/or stereo-control in the reaction products.[2] As additional advantages, these compounds are more stable than the corresponding ynamines,[3] owing to the presence of an electro-withdrawing group on the nitrogen atom, and, lastly, they can be synthesized by newly introduced and straightforward methodologies.

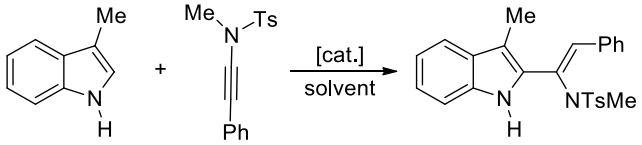
More recently, several gold complexes have been employed as electrophilic metal catalysts in reactions involving ynamides in inter[4] and intramolecular reactions.[5] In particular, after activation of the triple bond by the gold species, nucleophilic attack on the C_α is favored leading to the formation of vinyl-gold intermediates that can take part in other transformations (Scheme 1a). Gold mediated reactions involving ynamides have been often used for the synthesis and functionalization of heterocyclic compounds. In particular, C3 functionalization of C3 unsubstituted indoles via intermolecular alkyne oxidation[4m] and intramolecular cyclization of indoles bearing C3 tethered ynamides[5b] result in the synthesis, respectively, of linear and polycyclic derivatives (Scheme 1b, 1c).

Scheme 1. Gold-catalyzed Inter- and Intramolecular Reactions of Indoles with Ynamides



Taking these remarks into account and in accordance with our previous results in gold mediated synthesis and functionalization of indoles,[6] we decided to test the reactivity of indoles as nucleophiles in the gold catalyzed intermolecular reaction with ynamides under non-oxidative conditions. Reactions of C2/C3 unsubstituted indoles and of 2-substituted indoles with ynamides have been reported to occur under Brønsted acid catalysis affording regioselectively C3-*cis*-hydroarylated compounds.[7] Thus, in a preliminary set of experiments we tested the efficiency of [Au(JohnPhos)NTf_2] [JohnPhos = (2-biphenyl)di-*tert*-buthylphosphine] in the same reactions and the corresponding hydroarylated compounds were regioselectively obtained in moderate yields and in E/Z mixtures.[8] Thus, we turned our attention to C3 substituted indoles as they could react with ynamides through new reaction paths (Scheme 1d). Thus, 3-methylindole (**1a**) was reacted with an equimolecular amount of *N*-tosylynamide **2a** in the presence of [Au(JohnPhos)NTf_2] (5 mol %) in DCM at room temperature. After 24 h, compound **3a** was isolated as single stereoisomer in 35% yield, beside unreacted **1a** (Table 1, entry 1). The formation of compound **3a** is notable as indoles of general formula **3**, bearing an α-amidovinyl substituent at C2, have not yet been described in literature. Moreover, they pertain to the class of 2-vinylindoles, high valuable substrates for the synthesis of more complex derivatives via cycloaddition/cyclization reactions.[9] The novelty of the achieved transformation and the remarkable structure of the obtained compound prompted us to search for the best catalyst/solvent system for the synthesis of **3a** and to study the scope and the mechanism of the reaction. Therefore, using **1a** and **2a** in a model reaction, we optimized the conditions for the synthesis of **3a**. The obtained results are summarized in Table 1.

Table1. Screening of the reaction conditions for the synthesis of 3a.



1a **2a** **3a**

entry[a]	cat. (5 mol %)	solvent	*t* (°C)	Time (h)	Yield (%)[b]	Z/E[c]
1	Au(JohnPhos)NTf_2	DCM	rt	24	35	>20:1
2	Au(JohnPhos)NTf_2	DCE	80	6	72	>20:1
3	Au(IPr)NTf_2	DCE	80	6	57	>20:1
4	Au(PPh_3)NTf_2	DCE	80	6	58	1.4:1
5	Au(JohnPhos)SbF_6	DCE	80	6	56	>20:1
6	Au(JohnPhos)NTf_2	toluene	80	6	65	>20:1
7	Au(JohnPhos)NTf_2	toluene	110	6	59	>20:1
8	Au(JohnPhos)NTf_2	DCE	120, mw	0.5	69	>20:1
9	Au(JohnPhos)NTf_2	DCE	120, mw	0.25	75[d]	>20:1
10	Au(JohnPhos)NTf_2	toluene	120, mw	0.25	70[d]	>20:1
11	$AuCl_3$	DCE	80	6	5	>20:1
12	$AgNTf_2$	DCE	80	6	15[e]	>20:1
13	$PtBr_2$(cod)	DCE	80	6	–	–
14	$HNTf_2$ (10 mol %)	DCE	80	5	59	2.5:1

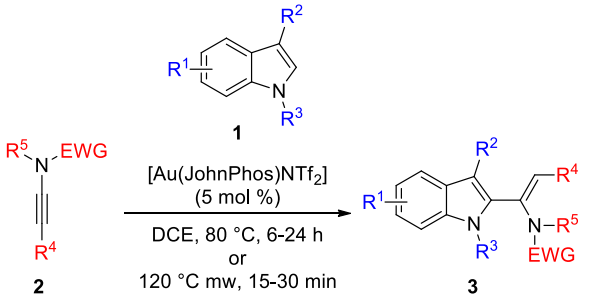
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (5 mol %), in the stated solvent (0.1 M). [b] Isolated yield. [c] Measured via ^{1}H-NMR. d1.1 equiv of **2a** were used. eIn mixture with an unidentified side-product. JohnPhos = (2-biphenyl)di-*tert*-buthylphosphine. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

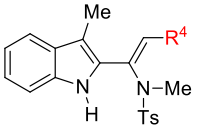
Starting from the preliminary result reported in entry 1, by increasing the temperature to 80 °C, in DCE, **3a** was formed in 72% yield, in a reduced reaction time of 6 h (entry 2). We next evaluated the influence of gold(I) species on the reaction outcome. Neither the use of carbenic [Au(IPr)NTf_2] or of [Au(PPh_3)NTf_2] had positive effect on the reaction yield. In addition, using PPh_3 as gold ligand, the reaction was not stereoselective and **3a** was isolated as an inseparable mixture of *Z/E* isomers with a ratio of 1.4/1 (entries 3, 4). Similarly, the use of [Au(JohnPhos)SbF_6(CH_3CN)] bearing a different counterion than triflimidate, was not leading to any improved result (entry 5). To evaluate the effect of both solvent and temperature, the reaction was conducted in toluene at 80 or 110 °C. Under these conditions, **3a** was isolated in 65% and 59% yield, respectively (entries 6, 7). To improve the efficiency of the reaction, we decided to modify the heating source by employing a microwave reactor.[10] Thus, the reaction conducted in the presence of [Au(JohnPhos)NTf_2] in DCE at 120 °C for 0.5 h, was leading to **3a** in 69% yield (entry 8). A shortened reaction time was even giving better results, **3a** was in fact formed in 0.25 h with 75% yield (entry 9). Similar results were obtained using toluene as solvent (entry 10). Besides gold(I) complexes, the activity of other metal catalysts was then evaluated. The use of both $AuCl_3$ and $AgNTf_2$ was

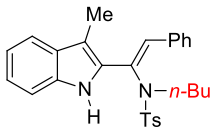
less effective and **3a** was isolated in poor yield (entries 11, 12). The reaction conducted under Pt(II) catalysis did not give rise to any product and both starting materials were recovered after 6 h at 80 °C (entry 13). Finally, we conducted the reaction in the presence of a Brønsted acid such as $HNTf_2$. In this case, product was isolated but in a lower yield of 59% and as *E/Z* isomer mixture with a ratio of 2.5:1 (entry 14).

Having the best reaction conditions in hands (Table 1, entries 2 and 9), we next explored the scope of the transformation (Scheme 2).

Scheme 2. Scope of the reaction between 1 and 2[a, b]

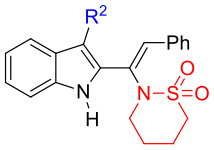


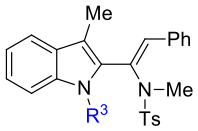




3g, 55%, (mw, 30'), Z/E = >20:1

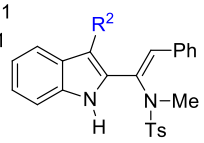
3b: R^4 = 3-F-C_6H_4, 70%, (mw, 15'), Z/E = >20:1
3c: R^4 = 4-Me-C_6H_4, 60%, (mw, 15'), Z/E = >20:1
3d: R^4 = 4-OMe-C_6H_4, 48%, (mw, 15'), Z/E = >20:1
3e: R^4 = *n*-Hex, 38%, (mw, 30'), Z/E = >20:1
3f: R^4 = *c*-Pent, 36%, (mw, 30'), Z/E = >20:1

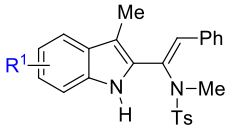




3l: R^3 = Bn, 65%, (mw, 15'), Z/E = >20:1
3m: R^3 = Me, 65%, (mw, 30')[c], Z/E = >20:1

3h: R^2 = Me, 87%, (20 h), Z/E = >20:1
76%, (cat. 2 mol%, 20 h), Z/E = >20:1
3i: R^2 = $(CH_2)_2OTIPS$, 61% (mw, 30'), Z/E = >20:1
3j: R^2 = $CH_2CH{=}CH_2$, 55%, (mw, 30'), Z/E = >20:1
3k: R^2 = $(CH_2)_2COCH_3$, 57%, (mw, 30'), Z/E = 9:1





3p: R^2 = $(CH_2)_2OTIPS$, 65%, (4 h), Z/E = >20:1
3q: R^2 = $CH_2CH{=}CH_2$ 56%, (mw, 30'), Z/E = >20:1
3r: R^2 = $(CH_2)_2COCH_3$, 53%, (mw, 30'), Z/E = 14:1

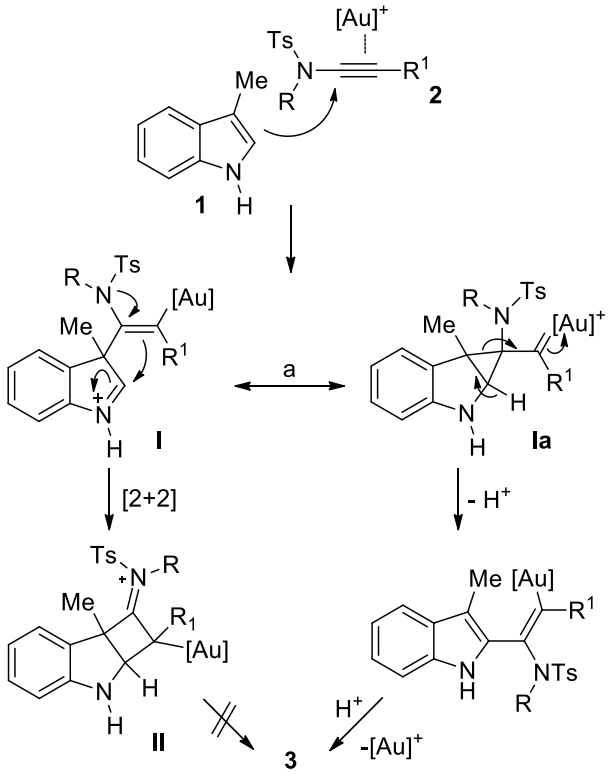
3n: R^1 =6-F, 88%, (24 h), Z/E = >20:1
3o: R^1 = 5-Me, 66%, (mw, 30'), Z/E = >20:1

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (5 mol %), in DCE (0.1 M). [b]Isolated Yield. [c]Reaction performed on 1 mmol scale.

At first, we focused our attention in the modification of the ynamide. The use of different substituents on the alkyne moiety was tolerated but the best results were obtained when R^4 was an aromatic ring. In those cases, the employment of electron-poor or electron-rich arenes was not particularly affecting the reaction outcome and products **3b**-**3d** were isolated in good yields. On the contrary, when R^4 was substituted with an alkyl group, the yield of the reaction decreased. Products **3e**, bearing an aliphatic alkyl chain and **3f** substituted with a secondary alkyl group, were in fact isolated in lower yield and required a prolonged reaction time. Next, the methyl group on the amide moiety was replaced by a *n*-butyl chain, affording **3g** in 55% yield. Furthermore, we used a cyclic aliphatic sulfonamide as electrowithdrawing substituent than the tosyl group, enabling the synthesis of **3h**, when R^4 is a phenyl ring, with high yield. Not only the ynamide **2** but also the nature of indole **1** could be varied. The reaction proceeded well by using *N*-benzylated or *N*-methylated 3-methylindole and the corresponding products **3l** and **3m** were obtained with good yield. Importantly, the synthesis **3m** was performed on 1 mmol scale without any significant variation on the formation of the final product. We evaluated the effect of various substituents on the benzene indole ring and when R^1 = 6-F the resulting fluorinated derivative **3n** was isolated in high yield. Similarly, when R^1 = Me, we got **3o** in 66% yield. Finally, we varied the substituent on C-3 of the indole ($R^2 \neq$ Me). The use of a TIPS-protected tryptophol was allowed yielding **3p** efficiently, while 3-allyl led to the formation of **3q**. We investigated also the possibility of employing 4-(1*H*-indol-3-yl)butan-2-one as starting material. In this case we were able to isolate **3r**, even if in a 14:1 mixture with the *E* isomer. These last indole derivatives were reacted with a cyclic aliphatic sulfonamide as well. Thus, TIPS-protected **3i** and allyl derivative **3j**, were synthetized with 61% and 55% yield, respectively. In addition, the reaction could also tolerate the presence of a ketone group, yielding **3k** in 57% yield but in 9:1 mixture with the *E* isomer. Finally, the reaction between **1a** and **2a** was repeated under conventional heating (table 1, entry 2) on multigram-scale (5 mmol of **1a**) and **3a** was obtained in comparable 76% yield.

The mechanism we propose for this transformation is reported in Scheme 3. Anti-addition of indole **1** and gold over the activated triple bond[11] of ynamide **2** give rise to intermediate **I** occurring in resonance with cyclopropyl gold-carbenoid **Ia**. Starting from **Ia**, concurrent loss of proton and cyclopropane ring opening followed by protodeauration step could give rise to **3** and restore the catalyst. The greater importance of structure resonance **Ia** compared to **I** is supported by the evidence that an alternative reaction path involving, starting from **I**, the intermediacy of a formal [2+2] cycloadduct **II** can be ruled out as it cannot give rise to **3**. Moreover, the proposed reaction mechanism is in accordance with literature data for similar processes.[11,12] In particular, the mechanism is in accordance with the proposal of Liu and coworkers for the gold-catalyzed intermolecular reactions of ynamides with electron-rich alkenes.[12a] Also in their experiments they did not find any evidence of the intermediacy of a [2+2] cycloadduct and the obtained products account for the intermediacy of a gold carbenoid specie.

Scheme 3. Proposed Reaction Mechanism



In summary, a new and straightforward synthesis of an original class of 2-vinylindoles was developed. As demonstrated by us and by others, 2-vinylindoles are particularly useful as inner-outer ring dienes in [4+2] (dearomative) cycloaddition/cyclization reactions.[9] In particular, compounds **3** present distinct electronic properties with respect to their well established and studied congeners and could be tested in dearomative [4+2] cyclization/cycloaddition reactions for the synthesis of polycyclic indoles.[13]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds;

Notes

The authors declare no competing financial interest.

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